



**University of
Zurich**^{UZH}

**Zurich Open Repository and
Archive**

University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2005

The mutational spectrum of PTPN11 in juvenile myelomonocytic leukemia and Noonan syndrome/myeloproliferative disease

Kratz, Christian P ; Niemeyer, Charlotte M ; Castleberry, Robert P ; Cetin, Mualla ; Bergsträsser, Eva ; Emanuel, Peter D ; Hasle, Henrik ; Kardos, Gabriela ; Klein, Cornelia ; Kojima, Seiji ; Sary, Jan ; Trebo, Monika ; Zecca, Marco ; Gelb, Bruce D ; Tartaglia, Marco ; Loh, Mignon L

Abstract: Germ line PTPN11 mutations cause 50% of cases of Noonan syndrome (NS). Somatic mutations in PTPN11 occur in 35% of patients with de novo, nonsyndromic juvenile myelomonocytic leukemia (JMML). Myeloproliferative disorders (MPDs), either transient or more fulminant forms, can also occur in infants with NS (NS/MPD). We identified PTPN11 mutations in blood or bone marrow specimens from 77 newly reported patients with JMML (n = 69) or NS/MPD (n = 8). Together with previous reports, we compared the spectrum of PTPN11 mutations in 3 groups: (1) patients with JMML (n = 107); (2) patients with NS/MPD (n = 19); and (3) patients with NS (n = 243). Glu76 was the most commonly affected residue in JMML (n = 45), with the Glu76Lys alteration (n = 29) being most frequent. Eight of 19 patients with NS/MPD carried the Thr73Ile substitution. These data suggest that there is a genotype/phenotype correlation in the spectrum of PTPN11 mutations found in patients with JMML, NS/MPD, and NS. This supports the need to characterize the spectrum of hematologic abnormalities in individuals with NS and to better define the impact of the PTPN11 lesion on the disease course in patients with NS/MPD and JMML.

DOI: <https://doi.org/10.1182/blood-2005-02-0531>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-66276>

Journal Article

Originally published at:

Kratz, Christian P; Niemeyer, Charlotte M; Castleberry, Robert P; Cetin, Mualla; Bergsträsser, Eva; Emanuel, Peter D; Hasle, Henrik; Kardos, Gabriela; Klein, Cornelia; Kojima, Seiji; Sary, Jan; Trebo, Monika; Zecca, Marco; Gelb, Bruce D; Tartaglia, Marco; Loh, Mignon L (2005). The mutational spectrum of PTPN11 in juvenile myelomonocytic leukemia and Noonan syndrome/myeloproliferative disease. *Blood*, 106(6):2183-2185.

DOI: <https://doi.org/10.1182/blood-2005-02-0531>

blood

2005 106: 2183-2185
Prepublished online May 31, 2005;
doi:10.1182/blood-2005-02-0531

The mutational spectrum of *PTPN11* in juvenile myelomonocytic leukemia and Noonan syndrome/myeloproliferative disease

Christian P. Kratz, Charlotte M. Niemeyer, Robert P. Castleberry, Mualla Cetin, Eva Bergsträsser, Peter D. Emanuel, Henrik Hasle, Gabriela Kardos, Cornelia Klein, Seiji Kojima, Jan Stary, Monika Trebo, Marco Zecca, Bruce D. Gelb, Marco Tartaglia and Mignon L. Loh

Updated information and services can be found at:

<http://bloodjournal.hematologylibrary.org/content/106/6/2183.full.html>

Articles on similar topics can be found in the following Blood collections

[Brief Reports](#) (1630 articles)

[Neoplasia](#) (4217 articles)

[Oncogenes and Tumor Suppressors](#) (795 articles)

[Signal Transduction](#) (1930 articles)

Information about reproducing this article in parts or in its entirety may be found online at:

http://bloodjournal.hematologylibrary.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:

<http://bloodjournal.hematologylibrary.org/site/misc/rights.xhtml#reprints>

Information about subscriptions and ASH membership may be found online at:

<http://bloodjournal.hematologylibrary.org/site/subscriptions/index.xhtml>

Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.

Copyright 2011 by The American Society of Hematology; all rights reserved.



Brief report

The mutational spectrum of *PTPN11* in juvenile myelomonocytic leukemia and Noonan syndrome/myeloproliferative disease

Christian P. Kratz, Charlotte M. Niemeyer, Robert P. Castleberry, Mualla Cetin, Eva Bergsträsser, Peter D. Emanuel, Henrik Hasle, Gabriela Kardos, Cornelia Klein, Seiji Kojima, Jan Stary, Monika Trebo, Marco Zecca, Bruce D. Gelb, Marco Tartaglia, and Mignon L. Loh

Germ line *PTPN11* mutations cause 50% of cases of Noonan syndrome (NS). Somatic mutations in *PTPN11* occur in 35% of patients with de novo, nonsyndromic juvenile myelomonocytic leukemia (JMML). Myeloproliferative disorders (MPDs), either transient or more fulminant forms, can also occur in infants with NS (NS/MPD). We identified *PTPN11* mutations in blood or bone marrow specimens from 77 newly reported patients with JMML (n = 69) or NS/MPD (n = 8). To-

gether with previous reports, we compared the spectrum of *PTPN11* mutations in 3 groups: (1) patients with JMML (n = 107); (2) patients with NS/MPD (n = 19); and (3) patients with NS (n = 243). Glu76 was the most commonly affected residue in JMML (n = 45), with the Glu76Lys alteration (n = 29) being most frequent. Eight of 19 patients with NS/MPD carried the Thr73Ile substitution. These data suggest that there is a genotype/phenotype correlation in the spectrum of *PTPN11*

mutations found in patients with JMML, NS/MPD, and NS. This supports the need to characterize the spectrum of hematologic abnormalities in individuals with NS and to better define the impact of the *PTPN11* lesion on the disease course in patients with NS/MPD and JMML. (Blood. 2005;106:2183-2185)

© 2005 by The American Society of Hematology

Introduction

The *PTPN11* proto-oncogene encodes Src-homology tyrosine phosphatase 2 (SHP-2), a protein tyrosine phosphatase with a role in signal transduction and hematopoiesis.^{1,2} Somatic *PTPN11* mutations exist in 35% of juvenile myelomonocytic leukemia (JMML) specimens and are less frequent in other leukemias.³⁻⁶ SHP-2 relays signals from activated growth factor receptors to Ras. *PTPN11*, *KRAS2*, *NRAS*, and *NF1* mutations are found in mutually exclusive subsets of patients with JMML.^{3,4} These data support the hypothesis that hyperactive Ras signaling plays a central role in JMML.

Germ-line *PTPN11* mutations cause approximately 50% of cases of Noonan syndrome (NS),^{7,8} a congenital disorder characterized by facial anomalies, short stature, and heart defects.⁹ Whereas NS is frequently inherited as an autosomal dominant condition, almost half of the constitutional *PTPN11* mutations found in NS arise sporadically. Germ-line *PTPN11* mutations are also found in patients with multiple lentigine syndrome (LS), a rare developmental disorder clinically related to NS.⁹ Infants with NS are predisposed to developing a myeloproliferative disorder (NS/MPD), which may regress without treatment or follow an aggressive clinical course similar to JMML.¹⁰⁻¹⁴ By contrast, cases of JMML

that arise in patients without NS have a poor prognosis without hematopoietic stem cell transplantation.¹⁵⁻¹⁸ Recent studies show that children with JMML have improved outcomes when they are treated aggressively early in the course of disease.¹⁸ Therefore, differentiating JMML from NS/MPD and identifying patients with NS/MPD who will require aggressive treatment are important clinical questions. We identify *PTPN11* mutations in 77 newly reported patients with JMML and NS/MPD, and compare the mutational spectrum in JMML, NS/MPD, and NS/LS to determine if genotype-phenotype correlations exist that may help guide diagnosis and clinical management.

Study design

Tissue samples (bone marrow, peripheral blood, and, rarely, buccal swab and skin fibroblasts) from patients with JMML and NS/MPD were collected under Institutional Review Board–approved protocols at each institution and with informed consent. DNA was extracted and analyzed for mutations in Freiburg, Germany; New York, New York; Rome, Italy; Nagoya, Japan; and San Francisco, CA. Since the data accumulated thus far have

From the Department of Pediatrics and Adolescent Medicine, University of Freiburg, Germany; Department of Pediatric Hematology/Oncology and Division of Hematology/Oncology, Comprehensive Cancer Center, University of Alabama at Birmingham, AL; Department of Pediatric Hematology, Ihsan Dogramaci Children's Hospital, Hacettepe University, Ankara, Turkey; Department of Pediatrics, Zurich, Switzerland; Department of Pediatrics, Skejby Hospital, Aarhus University, Denmark; Dutch Childhood Oncology Group, the Hague, the Netherlands; Department of Pediatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan; Department of Pediatrics, University Hospital Motol, Prague, Czech Republic; St Anna Children's Hospital, Vienna, Austria; Oncoematologia Pediatrica, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo, Pavia, Italy; Departments of Pediatrics and Human Genetics, Mount Sinai School of Medicine, New York, NY; Dipartimento di Biologia Cellulare e Neuroscienze, Istituto Superiore di Sanità, Rome, Italy; and Department of Pediatrics and the Comprehensive Cancer Center, University of California at San Francisco, CA.

Submitted February 8, 2005; accepted May 16, 2005. Prepublished online as

Blood First Edition Paper, May 31, 2005; DOI 10.1182/blood-2005-02-0531.

Supported by the Deutsche José Carreras Leukämie Stiftung e.V. (C.P.K., C.K.), and by a Translational Research Award (6021-99) from the Leukemia and Lymphoma Society (R.P.C.), Telethon-Italy grant GGP04172 (M.T.), by the Cancer Research Coordinating Committee, the Frank A. Campini Foundation and the Hope Street Kids Foundation (M.L.L.), and by US Public Health Service grants R01 CA95621 (P.D.E., R.P.C., M.L.L.), K24 CA80916 (P.D.E.), HL71207, HD01294, HL074728 (B.D.G.), P30 CA82103, and R01 CA104282 (M.L.L.) from the National Institutes of Health.

Reprints: Mignon L. Loh, University of California, Room HSE-302 Box 0519, San Francisco, CA 94143; e-mail: loh@itsa.ucsf.edu.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 U.S.C. section 1734.

© 2005 by The American Society of Hematology

Table 1. *PTPN11* mutations in 77 newly reported children with JMML or NS/MPD

Cohort, no. cases	Nucleotide substitution	Amino acid substitution
JMML, N = 69		
1	155C > G*	Thr52Ser
1	178G > C	Gly60Arg
9	179G > T	Gly60Val
6	181G > T	Asp61Tyr
6	182A > T	Asp61Val
1	182A > G	Asp61Gly
5	214G > A	Ala72Thr
4	215C > T	Ala72Val
20	226G > A	Glu76Lys
6	227A > G	Glu76Gly
1	226-227GA > AT*	Glu76Met
5	1508G > C	Gly503Ala
4	1508G > T	Gly503Val
NS/MPD, N = 8		
2	182A > G	Asp61Gly
1	215C > G	Ala72Gly
2	218C > T	Thr73Ile
1	1492C > T	Arg498Trp
1	1504T > G*	Ser502Ala
1	1517A > C	Gly506Pro

*Novel mutation.

demonstrated that *PTPN11* mutations in myeloproliferative disorders occur in exons 3 (~90%) or 13 (~10%).^{3,4} these were the only exons screened in many of the European and American cases as previously described.^{3,4,8} Mutations in the JMML cases from Nagoya were detected by analyzing exons 3, 8, and 13 employing standard cloning and sequencing techniques.

Results and discussion

Results of the *PTPN11* mutational screening performed on the 77 newly reported patients (JMML = 69, NS/MPD = 8) are listed in Table 1. Two mutations, 155C > T (Thr52Ser) and 226-227GA > AT (Glu76Met), had not been previously documented in JMML or other malignancies.^{3-6,19,20} Figure 1 shows an updated compendium of *PTPN11* mutations previously documented in JMML or NS/MPD combined with the current cohort of 77 newly reported patients. The series includes 107 JMML cases, 19 patients with NS/MPD, and 243 patients with NS or LS. While other exons are commonly mutated in the germ line of patients with NS and LS, only cases with exon 3 and 13 mutations are listed in Figure 1.

All defects with the exception of 2 result in an amino acid substitution. While there is overlap with respect to the substitutions

seen in patients with NS/MPD and NS (Figure 1; Asp61Gly, Tyr62Asp, Ala72Gly, Thr73Ile, Ser502Thr, and Gly503Arg) or LS (Arg498Trp, Gln506Pro), only the Asp61Gly mutation is shared among patients with JMML, NS/MPD, and NS. Remarkably, 45 (42%) of the mutations found in JMML cases alter codon 76. Mutations affecting Glu76 are rare in individuals with NS (< 3% of cases), but are conservative (Glu76Asp) when they occur.

We identified a 214G > A (Ala72Thr) mutation in the bone marrow specimen of a 5-month-old girl with JMML for whom umbilical cord was collected at birth. Remarkably, the cord blood contained the same *PTPN11* mutation, which was absent in the child's buccal cells and parental DNA. Despite the assumption that JMML arises in utero, this is, to our knowledge, one of the first demonstrations that a somatically acquired JMML-associated *PTPN11* mutation occurred before birth.

In this newly reported cohort of 77 patients (Table 1), 6 missense changes, including 1 novel mutation affecting exon 13, 1504T > G (Ser502Ala), were identified in 8 NS/MPD specimens. We had buccal swab DNA (n = 2) and skin fibroblast DNA (n = 1) available for analysis from 3 patients and confirmed the presence of the *PTPN11* mutation in each case, supporting the germ-line origin of the lesion. Together with previous data, the Thr73Ile substitution was identified in 8 out of 19 NS/MPD cases (Figure 1), representing the most common mutation in patients with NS/MPD. This mutation is uncommon in NS patients without MPD, and has not been observed among patients with JMML.

Analysis of DNA from the unaffected parents of 3 children with NS/MPD with different *PTPN11* mutations (Asp61Gly, Ser502Ala, and Gly506Pro) demonstrated the sporadic origin of each lesion. Consistent with these results, all previous children with NS/MPD carrying a mutated *PTPN11* gene have been documented to be sporadic cases.^{3,14} These findings suggest that NS/MPD is associated with mutations that might be associated with decreased fertility or have more severe consequences on fetal survival. This is consistent with the observation that mutations associated with NS/MPD have only rarely been identified in patients with familial NS cases, and that mutants detected in families transmitting NS are unlikely to be associated with NS/MPD.^{7,21-25}

We identified 1 patient with JMML carrying a somatic 182A > G (Asp61Gly) mutation previously associated with NS.⁷ The mutation was found in hematopoietic cells but was absent in skin fibroblasts. The same mutation was found in 2 patients with NS/MPD. In one of the latter patients the germ-line nature of this lesion was confirmed by analyzing buccal cells. To our knowledge, the 182A > G (Asp61Gly) mutation is the only *PTPN11* mutation associated with JMML, NS/MPD, and NS.

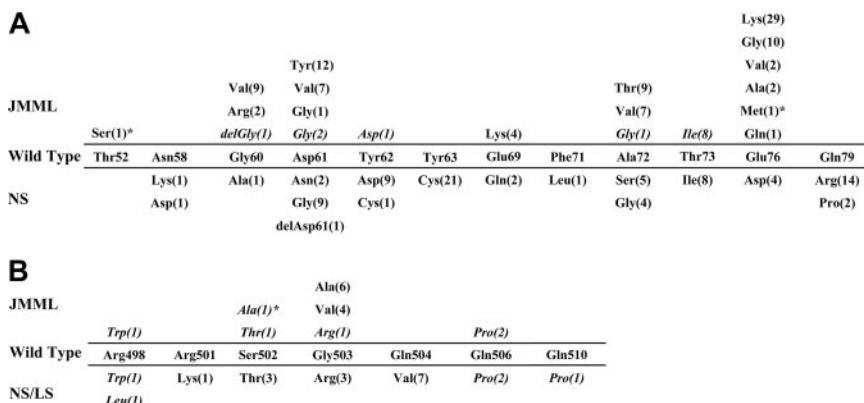


Figure 1. *PTPN11* mutations in JMML, NS/MPD, and NS/LS. The middle sections of both panels show wild-type SHP2 amino acid residue at each position. (A) Residues located within the N-SH2 domain encoded by exon 3. (B) Residues located within the portion of the catalytic domain encoded by exon 13. Amino acid substitutions documented in JMML and NS/MPD (italics), and in NS and LS (italics) are shown above and below the wild-type SHP2 sequence, respectively. Del indicates a deletion of this amino acid. Digits in parentheses indicate the numbers of individuals with JMML, NS/MPD, or NS carrying a specific mutation. Novel mutations are identified by asterisks. Whereas virtually all mutations in JMML and NS/MPD are located within these confined regions, mutations associated with NS alone alter other residues of SHP2 in approximately 50% of the cases.⁹ Our data, updated to January 2005, includes 107 cases with JMML, 19 with NS/MPD, 181 with NS, and 42 with LS.

The finding of Asp61Gly in JMML and NS/MPD is intriguing as this substitution was used to generate a mouse knock-in model of NS.²⁶ When homozygous, the Asp61Gly mutant is embryonic lethal, whereas heterozygotes have decreased viability. Of note, while the JMML-like picture in infants with NS usually develops at or shortly after birth, *Ptpn11*^{Asp61Gly/+} mice show signs of a mild myeloproliferative disorder and splenomegaly by 5 months of age.

Similar to what is observed in NS, the vast majority of mutations identified in JMML and NS/MPD alter residues located at the interface between the N-terminal Src homology 2 (N-SH2) and catalytic (protein tyrosine phosphatase [PTP]) domains.²⁷ They are predicted to promote SHP-2 gain of function by impairing the switch between the active and inactive conformation of the protein, favoring a shift in the equilibrium toward the former. One exception is the Thr52Ser substitution, which affects the N-SH2 phosphotyrosyl-binding site.²⁷ It has been hypothesized that the genotype-phenotype relationships observed in patients with somatic and germ line mutations of *PTPN11* are due to distinct gain-of-function effects on the protein product SHP-2.³ Consistent with this view, somatically acquired JMML-associated *PTPN11* mutations are predicted to have a strong gain-of-function effect that might otherwise affect embryonic/fetal development if transmitted in the germ line, explaining why these mutations are not seen in NS. In contrast, germ-line mutations identified in NS are predicted to have weaker hematologic effects. It is also possible that the rare germ-line *PTPN11* lesions observed in NS/MPD can exhibit intermediate effects. Indeed, in vitro and in vivo experiments on

primary hematopoietic cells and cell lines show that somatic mutants confer more pronounced effects on cell growth than common mutants only found in NS,²⁸⁻³⁰ and exhibit an increased phosphatase activity basally.³

Our data raise a number of new questions. First, are somatic *PTPN11* mutations sufficient to initiate MPD and, if not, what are the cooperating molecular lesions? Second, do specific *PTPN11* mutations have different consequences depending on whether they involve the entire hematopoietic compartment or arise as clonal events? Third, do some patients with NS and *PTPN11* mutations develop transient myeloproliferation, which is unrecognized? Finally, does the nature of a *PTPN11* mutation (germ-line versus somatic) and the specific amino acid substitution detected provide information that can be used to guide decisions regarding the need to initiate aggressive treatment in infants presenting with JMML? These questions will be answered through ongoing collaborations between laboratory researchers and clinical investigators who are evaluating and treating children with these disorders.

Acknowledgments

The authors wish to thank all of the patients, families, and referring physicians who contributed samples to the investigators. We wish to acknowledge the National Children's Cancer Foundation on behalf of the samples collected in the United States.

References

- Neel BG, Gu H, Pao L. The 'Shp'ing news: SH2 domain-containing tyrosine phosphatases in cell signaling. *Trends Biochem Sci*. 2003;28:284-293.
- Tartaglia M, Niemeyer CM, Shannon KM, Loh ML. SHP-2 and myeloid malignancies. *Curr Opin Hematol*. 2004;11:44-50.
- Tartaglia M, Niemeyer CM, Fragale A, et al. Somatic mutations in PTPN11 in juvenile myelomonocytic leukemia, myelodysplastic syndromes and acute myeloid leukemia. *Nat Genet*. 2003;34:148-150.
- Loh ML, Vattikuti S, Schubert S, et al. Mutations in PTPN11 implicate the SHP-2 phosphatase in leukemogenesis. *Blood*. 2004;103:2325-2331.
- Loh ML, Reynolds MG, Vattikuti S, et al. PTPN11 mutations in pediatric patients with acute myeloid leukemia: results from the Children's Cancer Group. *Leukemia*. 2004;18:1831-1834.
- Tartaglia M, Martinelli S, Cazzaniga G, et al. Genetic evidence for lineage-related and differentiation stage-related contribution of somatic PTPN11 mutations to leukemogenesis in childhood acute leukemia. *Blood*. 2004;104:307-313.
- Tartaglia M, Mehler EL, Goldberg R, et al. Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. *Nat Genet*. 2001;29:465-468.
- Tartaglia M, Kalidas K, Shaw A, et al. PTPN11 mutations in Noonan syndrome: molecular spectrum, genotype-phenotype correlation, and phenotypic heterogeneity. *Am J Hum Genet*. 2002;70:1555-1563.
- Tartaglia M, Gelb BD. Noonan syndrome and related disorders: genetics and pathogenesis. *Annu Rev Genomics Hum Genet*. In press. 2005.
- Bader-Meunier B, Tchernia G, Mielot F, et al. Occurrence of myeloproliferative disorder in patients with Noonan syndrome. *J Pediatr*. 1997;130:885-889.
- Fukuda M, Horibe K, Miyajima Y, Matsumoto K, Nagashima M. Spontaneous remission of juvenile chronic myelomonocytic leukemia in an infant with Noonan syndrome. *J Pediatr Hematol Oncol*. 1997;19:177-179.
- Choong K, Freedmann MH, Chitayat D, Kelly EN, Taylor G, Zipusky A. Juvenile myelomonocytic leukemia and Noonan syndrome. *J Pediatr Hematol Oncol*. 1999;21:523-537.
- Silvio F, Carlo L, Elena B, Nicoletta B, Daniela F, Roberto M. Transient abnormal myelopoiesis in Noonan syndrome. *J Pediatr Hematol Oncol*. 2002;24:763-764.
- Yoshida R, Miyata M, Nagai T, Yamazaki T, Ogata T. A 3-bp deletion mutation of PTPN11 in an infant with severe Noonan syndrome including hydrops fetalis and juvenile myelomonocytic leukemia. *Am J Med Genet*. 2004;128A:63-66.
- Niemeyer CM, Arico M, Basso G, et al. Chronic myelomonocytic leukemia in childhood: a retrospective analysis of 110 cases. European Working Group on Myelodysplastic Syndromes in Childhood (EWOG-MDS). *Blood*. 1997;89:3534-3543.
- Niemeyer CM, Kratz C. Juvenile myelomonocytic leukemia. *Curr Oncol Rep*. 2003;5:510-515.
- Emanuel PD. Juvenile myelomonocytic leukemia. *Curr Hematol Rep*. 2004;3:203-209.
- Locatelli F, Nollke P, Zecca M, et al. Hematopoietic stem cell transplantation (HSCT) in children with juvenile myelomonocytic leukemia (JMML): results of the EWOG-MDS/EBMT trial. *Blood*. 2005;105:410-419.
- Loh ML, Martinelli S, Cordeddu V, et al. Acquired PTPN11 mutations occur rarely in adult patients with myelodysplastic syndromes and chronic myelomonocytic leukemia. *Leuk Res*. 2005;29:459-462.
- Bentires-Alj M, Paez JG, David FS, et al. Activating mutations of the Noonan syndrome-associated SHP2/PTPN11 gene in human solid tumors and adult acute myelogenous leukemia. *Cancer Res*. 2004;64:8816-8820.
- Yoshida R, Hasegawa T, Hasegawa Y, et al. Protein-tyrosine phosphatase, nonreceptor type 11 mutation analysis and clinical assessment in 45 patients with Noonan syndrome. *J Clin Endocrinol Metab*. 2004;89:3359-3364.
- Musante L, Kehl HG, Majewski F, et al. Spectrum of mutations in PTPN11 and genotype-phenotype correlation in 96 patients with Noonan syndrome and five patients with cardio-facio-cutaneous syndrome. *Eur J Hum Genet*. 2003;11:201-206.
- Kosaki K, Suzuki T, Muroya K, et al. PTPN11 (protein-tyrosine phosphatase, nonreceptor-type 11) mutations in seven Japanese patients with Noonan syndrome. *J Clin Endocrinol Metab*. 2002;87:3529-3533.
- Zenker M, Buheite G, Rauch R, et al. Genotype-phenotype correlations in Noonan syndrome. *J Pediatr*. 2004;144:368-374.
- Maheshwari M, Belmont J, Fernbach S, et al. PTPN11 mutations in Noonan syndrome type I: detection of recurrent mutations in exons 3 and 13. *Hum Mutat*. 2002;20:298-304.
- Araki T, Mohi MG, Ismat FA, et al. Mouse model of Noonan syndrome reveals cell type- and gene dosage-dependent effects of Ptpn11 mutation. *Nat Med*. 2004;10:849-857.
- Hof P, Pluskey S, Dhe-Paganon S, Eck MJ, Shoelson SE. Crystal structure of the tyrosine phosphatase SHP-2. *Cell*. 1998;92:441-450.
- Mohi MG, Williams IR, Dearolf CR, et al. Prognostic, therapeutic, and mechanistic implications of a mouse model of leukemia evoked by Shp2 (PTPN11) mutations. *Cancer Cell*. 2005;7:179-191.
- Chan RJ, Leedy MB, Munugalavada V, et al. Human somatic PTPN11 mutations induce hematopoietic cell hypersensitivity to granulocyte-macrophage colony stimulating factor. *Blood*. 2005;105:3737-3742.
- Schubert S, Lieu K, Rowe SL, et al. Functional analysis of leukemia-associated PTPN11 mutations in primary hematopoietic cells. *Blood*. Prepublished on March 10, 2005, as DOI 10.1182/blood-2004-11-4207. (Now available as *Blood*. 2005;106:311-317).